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10/053,530	01/17/2002	Jeffrey A. Ledbetter	390069.401	8993

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EXAMINER
HELMS, LARRY RONALD

ART UNIT	PAPER NUMBER
1642	

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13

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/053,530	Applicant(s) LEDBETTER ET AL.	
	Examiner Larry R. Helms	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *15-18 and 20-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group I, claims 1-14 and 19 in Paper No. 11 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 15-18, and 20-22 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions. Election was made in Paper No. 11.

3. Claims 1-14 and 19 are under examination.

Specification

4. The disclosure is objected to because of the following informalities:

a. The first line of the specification needs to be updated to indicate the provisional application which the instant application is claiming priority to.

b. The specification contains numerous places where the SEQ ID NOs are left blank, see for example page 14.

c. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code, see for example page 36, line 11. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

d. The brief description of the drawings need to indicate Figure 1A and B, Figure 6A and B, Figure 19A, B , and C.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-14 and 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1-14 and 19 are indefinite for reciting "derived" in claims 1, 4, 6, 7. The term "derived" is not one which has a universally accepted meaning in the art nor is it one which has been adequately defined in the specification. The primary deficiency in the use of this phrase is the absence of a ascertainable meaning for said phrase. Since it is unclear how the hinge regions are to be derivatized to yield the class of derivatives referred to in the claims, there is no way for a person of skill in the art to ascribe a discrete and identifiable class of compounds to said phrase. Further, it is not clear whether the "derived" hinge is formed by attachment of a detectable marker, therapeutic molecule, some other molecule or altering the amino acid sequence, for examples. In addition, since the term "derived" does not appear to be clearly defined in the

specification, and the term can encompass proteins with amino acid substitutions, insertions, or deletions, chemically derivatized molecules, or even mimetics. In absence of a single defined art recognized meaning for the phrase and lacking a definition of the term in the specification, one of skill in the art could not determine the metes and bounds of the claims.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 3 and 14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a binding domain-immunoglobulin fusion protein comprising a binding domain polypeptide which comprises an immunoglobulin light and heavy variable domain, does not reasonably provide enablement for a binding domain-immunoglobulin fusion protein comprising a binding domain polypeptide which comprises either an immunoglobulin light or heavy variable domain. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the

breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to a binding domain polypeptide that has either a heavy chain or a light chain which would not bind antigen. The specification teaches a binding domain comprising both a heavy chain and a light chain (see figure 8 and pages 14-15 and Examples). The specification does not enable a binding domain with only a heavy or a light chain.

It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding

myeloma protein resulted in the loss of antigen-binding function. It is unlikely that fusion proteins as defined by the claims which may contain less than the full complement of CDRs from the heavy and light chain variable regions of an antibody or both heavy and light chains have the required binding function. The specification provides no direction or guidance regarding how to produce fusion proteins and antibodies as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone.

Therefore, in view of the lack of guidance in the specification and in view of the discussion above one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

10. Claims 1-3, 5, 7-11, 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Shan et al (The Journal of immunology 162:6589-6595, 1999, IDS #7).

The claims recite a binding domain-immunoglobulin comprising a variable heavy and light chains that bind CD20 fused to a mutated hinge that contains no cysteine and a CH2 and CH3 domain and the fusion protein is capable of complement fixation or antibody dependent cell-mediated cytotoxicity and the mutated hinge region exhibits reduced ability to dimerize and the VH and VL are connected by a linker of SEQ ID NO:21 or three repeats of SEQ ID NO:21 and a pharmaceutical composition comprising such.

Shan et al teach a scFv that binds CD20 that has the recited linker and the scFv is fused to a hinge that has the cysteines removed and it can not dimerize and the hinge is fused to a CH2 and CH3 and since the fusion protein has the hinge, CH2 and CH3 it is inherent that the protein has complement fixation or dependent cell-mediated cytotoxicity. Shan et al also teach a composition with a physiological buffer (see entire document and see page 6590).

11. Claims 1-4, 7-8, 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Bodmer et al (U. S. Patent 5,677,425, issued 10/97).

Claims 2-3, 7-8 and 19 have been described supra. Claims 1 and 4 recite a mutated hinge region that contains one cysteine and the VH and VL is from a human immunoglobulin.

Bodmer et al teach an antibody wherein the hinge region is modified to have one cysteine and the variable regions and the constant regions can be humanized (see column 1, lines 25-33 and column 3, lines 14-67). Since the hinge has only one

cysteine it would be inherent that it would have a reduced ability to dimerize and since the fusion protein has the hinge, CH2 and CH3 it is inherent that the protein has complement fixation or dependent cell-mediated cytotoxicity.

12. Claims 1, 3, 8, 12, 19 are rejected under 35 U.S.C. 102(e) as being anticipated by Morrison et al (U.S. Patent 6,284,536, with priority to 4/98).

Claims 3, 8, and 19 have been described supra. Claim 1 and 12 recite a human IgA hinge in the fusion protein.

Morrison et al teach an antibody that has an IgA hinge. Since the antibody has the hinge, CH2 and CH3 it is inherent that the protein has complement fixation or dependent cell-mediated cytotoxicity.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 1-11 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shan et al (The Journal of immunology 162:6589-6595, 1999, IDS #7) as applied to claims 1-3, 5, 7-11, 19 above, and further in view of Bodmer et al (U. S.Patent 5,677,425, issued 10/14/97).

Claims 1-5, 7-11 and 19 have been described supra. Claim 6 recites VH and VL from a human immunoglobulin.

Shan et al has been described supra. Shan et al also teach making antibodies smaller while retaining bivalent binding properties (see page 6594). Shan et al does not teach a mutated hinge region containing one cysteine or a variable region from a human immunoglobulin. These deficiencies are made up for in the teachings of Bodmer et al.

Bodmer et al has been described supra and Bodmer et al teach mutations to reduce the cysteines in the hinge have the advantage that it will facilitate assembly of the antibody molecules (see column 3, lines 60-63).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have used the hinge region of Bodmer et al in the construct of Shan et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the hinge region of Bodmer et al in the construct of Shan et al because Shan et al teach that they are focusing on making antibodies that are bivalent. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the hinge region of Bodmer et al in the construct of Shan et al because Bodmer et al teach reducing the cysteine residues in the hinge to one facilitates assembly of antibody molecules. Thus, it would have been obvious to one of ordinary skill in the art to have used the hinge region of Bodmer et al which has a single cysteine residue and substitute this hinge for the hinge in Shan et al in order to produce an antibody which had the affinity of an intact antibody because it would have two binding sites.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

15. Claims 1-12 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shan et al (The Journal of immunology 162:6589-6595, 1999, IDS #7) as applied to claims 1-3, 5, 7-11, 19 above, and further in view of Bodmer et al (U. S.Patent 5,677,425, issued 10/14/97) and Morrison et al (U.S. Patent 6,284,536, priority to 4/98)

The claims have been described supra.

Shan et al has been described supra. Shan et al also teach making antibodies smaller while retaining bivalent binding properties (see page 6594). Shan et al does not teach a mutated hinge region containing one cysteine or a IgA hinge or mutated IgA hinge or a variable region from a human immunoglobulin. These deficiencies are made up for in the teachings of Bodmer et al and Morrison et al.

Bodmer et al has been described supra and Bodmer et al teach mutations to reduce the cysteines in the hinge have the advantage that it will facilitate assembly of the antibody molecules (see column 3, lines 60-63).

Morrison et al teach an antibody that has an IgA hinge.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have used the hinge region of Morrison et al or mutate the hinge regions as taught by Bodmer et al in the construct of Shan et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the hinge region of Morrison et al or mutate the hinge regions as taught by Bodmer et al in the construct of Shan et al because Shan et al teach that they are focusing on making antibodies that are bivalent. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the hinge region of Morrison et al or mutate the hinge regions as taught Bodmer et al in the construct of Shan et al because Bodmer et al teach reducing the cysteine residues in the hinge to one facilitates assembly of antibody molecules. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the hinge

region of Morrison et al or mutate the hinge regions as taught by Bodmer et al in the construct of Shan et al because Morrison et al teach the benefits of an IgA Fc and specifically an IgA with a hinge region. Thus, it would have been obvious to one of ordinary skill in the art to have used the hinge region of Morrison et al or mutate the IgA hinge region as taught by Bodmer et al which has a single cysteine residue and substitute this hinge for the hinge in Shan et al in order to produce an antibody which had the affinity of an intact antibody because it would have two binding sites.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

16. Claims 1-14 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shan et al (The Journal of immunology 162:6589-6595, 1999, IDS #7) as applied to claims 1-3, 5, 7-11, 19 above, and further in view of Bodmer et al (U. S.Patent 5,677,425, issued 10/14/97), Morrison et al (U.S. Patent 6,284,536, priority to 4/98) and Armitage et al (U.S. Patent 6,264,951, filed 12/96).

Claims 1-12 have been described supra. Claims 13 and 14 recite the binding domain comprises a CD154 extracellular domain and at least one immunoglobulin variable domain.

Shan et al has been described supra. Shan et al also teach making antibodies smaller while retaining bivalent binding properties (see page 6594). Shan et al does not teach a mutated hinge region containing one cysteine or a IgA hinge or mutated IgA hinge or a variable region from a human immunoglobulin or the extracellular domain of

CD154 or a fusion protein of CD154 and an immunoglobulin domain. These deficiencies are made up for in the teachings of Bodmer et al, Morrison et al, and Armitage et al

Bodmer et al has been described supra and Bodmer et al teach mutations to reduce the cysteines in the hinge have the advantage that it will facilitate assembly of the antibody molecules (see column 3, lines 60-63).

Morrison et al teach an antibody that has an IgA hinge.

Armitage et al teach a CD154 (CD40L) fused to an Fc and divalent CD40L fusions to heavy and light chains of antibodies to form oligomers (see column 7-10).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have used the hinge region of Morrison et al or mutate the hinge regions as taught by Bodmer et al in the construct of Shan et al and fuse the extracellular domain of CD154 to the construct.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the hinge region of Morrison et al or mutate the hinge regions as taught by Bodmer et al in the construct of Shan et al and fuse the extracellular domain of CD154 to the construct because Shan et al teach that they are focusing on making antibodies that are bivalent. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the hinge region of Morrison et al or mutate the hinge regions as taught Bodmer et al in the construct of Shan et al and fuse the extracellular domain of CD154 to the construct because Bodmer et al teach reducing the cysteine residues in

the hinge to one facilitates assembly of antibody molecules. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the hinge region of Morrison et al or mutate the hinge regions as taught by Bodmer et al in the construct of Shan et al and fuse the extracellular domain of CD154 to the construct because Morrison et al teach the benefits of an IgA Fc and specifically an IgA with a hinge region. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the hinge region of Morrison et al or mutate the hinge regions as taught by Bodmer et al in the construct of Shan et al and fuse the extracellular domain of CD154 to the construct because Armitage et al teach oligomers of CD40L are made with both the heavy chain and light chains of antibodies and form oligomers. Thus, it would have been obvious to one of ordinary skill in the art to have used the hinge region of Morrison et al or mutate the IgA hinge region as taught by Bodmer et al which has a single cysteine residue and substitute this hinge for the hinge in Shan et al and conjugate the extracellular domain of CD154 in order to produce a fusion protein which had the affinity of an intact antibody because it would have two binding sites and the molecule would be divalent .

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

17. No claim is allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

19. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4242.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879